UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,501	09/10/2003	Ned M. Weinshenker	MCP-1	7515

24039 7590 09/13/2005

INNOVAR, LLC
P O BOX 250647
PLANO, TX 75025

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 09/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,501	WEINSHENKER ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-21 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-21 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 10 September 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 09172004,09132004;.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims read upon pharmaceutical compositions comprising an anti-tumor drug and cobalamin conjugate; however, one of ordinary skill in the art would not be apprised of the metes and bounds of the instant invention as the components of the anti-tumor drug and cobalamin conjugate are only described in functional terms. The terms "drug is cleavable from the linker and/or the linker is cleavable from the drug by an intracellular membrane after complexation with transcobalamin", "the conjugate is adapted for transport across a cellular membrane after complexation with transcobalamin", "the conjugate is cleavable by an intracellular enzyme", "conjugate possesses reduced systemic toxicity as compared to the corresponding free anti-tumor drug", "divalent functional group", "non-peptide residue", "divalent carbonyl", "conjugate posses improved efficacy", and "functional groups comprises a derivatizable site on DG" are not sufficient to convey a chemical structure, chemical name or the like to the instantly claimed conjugate. There is nothing inherently wrong with defining some part of an invention in functional terms; however, a functional limitation must be evaluated

and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. Functional descriptions of chemical compounds/compositions must be coupled with a known or disclosed correlation between function and structure.

3. Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 8, the parenthetical phrase "(R is =O, =S or =NH)" renders the claim indefinite because it is unclear whether the limitations within the parentheses are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 9, the phrases "such as" and "as well as" render the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any

inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Grissom et al. US 6,797,521 (Grissom), Toki et al. J. Org. Chem. (2002), Vol. 67, pages 1866-1872 (Toki), Dubowchik et al. Bioorganic & Medicinal Chemistry Letters (1998), Vol. 8, pages 3341-3346 (Dubowchik), and Habberfield et al. US 5,574,018 (Habberfield).

Claims 1-5 and 7-20 are drawn to an anti-tumor drug and cobalamin conjugate comprising a cobalamin, or a derivative or analogue thereof; a linker covalently bound to the 5'-OH moiety of cobalamin or cobalamin derivative; and an anti-tumor drug covalently bound to the linker thereby forming the conjugate.

Claims 6 and 21 are drawn to a method of treating a tumor using the instantly claimed anti-tumor drug and cobalamin conjugate.

Grissom teaches that a doxorubicin-cobalamin conjugate was synthesized as a potential chemotherapeutic compound (column 5, line 55 to column 6, line 5). Cellular uptake of the doxorubicin-cobalamin conjugate can be observed in P-388 murine leukemia cells, as well as in HCT-116 human colon tumor cells.

Grissom differs from the instantly claimed compound in that Grissom is silent on the chemical structure of the doxorubicin-cobalamin conjugate; however, the instantly claimed anti-tumor drug and cobalamin conjugate would have been obvious to one of ordinary skill in the art at the time of the invention in view of the teachings of Dubowchik, Habberfield and Toki.

Toki teaches that peptide-containing anticancer prodrugs have been developed that are activated by proteases within solid tumors (pages 1866-1867). The drugs can be appended directly to the peptide, leading to prodrugs that can either release the parent drug or a drug that contains vestiges of the bound peptide. In the latter case, the released drug may have impaired cytotoxic activity. An additional consideration for direct drug attachment to peptides is the negative influence the drug can have on the kinetics of peptide hydrolysis. To circumvent these potential shortcomings, an alternative approach for drug attachment incorporates the use of self-immolative spacers that spatially separate the drug from the site of enzymatic cleavage. The subsequent collapse of the incorporated linkers allows for the elimination of the fully active, chemically unmodified drug from the conjugate upon amid bond hydrolysis. One of the most

commonly used spacers is the bifunctional p-aminobenzyl alcohol group, which is linked to the peptide through the amine moiety, forming an amide bond. Amine-containing drugs are attached through carbamate functionalities to the benzylic hydroxyl group of the linker. The resulting prodrugs are activated upon protease-mediated cleavage, leading to a 1,6-elimination reaction that releases the unmodified drug, carbon dioxide, and remnants of the linker group.

Dubowchik teaches peptide-DOX (doxorubicin) substrates that contain a self-immolative PABC spacer that are efficiently cleaved by cathepsin B to release free DOX but are very stable in human plasma (page 3345). Cathepsin B is an attractive target for release of drugs from conjugates that are taken up by receptor-mediated endocytosis since it is ubiquitous and found in relatively high levels in mammalian lysosomes. In addition, several of these compounds release DOX on a time scale that may make them useful as prodrugs for metastatic or primary tumors that express extracellular cathepsin B.

Habberfield teaches that the gastrointestine (i.e. G.I.) is an organ of the body that functions to physically, chemically and enzymatically process and break down ingested nutrients (columns 1-3). Uptake of nutrients, or more specifically their digestive products, takes place principally in the small intestine. The intestine is lined with a mucus layer. The mucus layer acts as a barrier to macromolecules, e.g., molecules having a molecular weight of greater than 17 kilodaltons. Thus, the lining of the intestine serves as an efficient barrier to both lipophilic and hydrophilic molecules. As a consequence, the oral administration of a large, macromolecular therapeutical compound is normally limited as to

effectiveness. However, some molecules are specifically taken up in the G.I. tract as a normal function of the digestive process. Of special interest here is the biological mechanism for the uptake of vitamin B12. It has been proposed that this vitamin B12 mechanism may be utilized to transport biologically active substances such as drugs, hormones, antigenic material, and the like, from the intestinal lumen into circulatory blood by covalently couplings these substances to vitamin B12. Habberfield further teaches conjugates formed using a chemical approach involving covalently linking vitamin B12 to a therapeutic compound (protein) via the primary (5') hydroxyl group of the ribose moiety of vitamin B12. The resulting conjugates are capable of administration to mammals through various modes of delivery, preferably oral. In general, biologically active conjugates are prepared by reacting the therapeutically active compound with 5'-O-[glutaroyl]cyanocobalamin under conditions which form covalent bonds between the two. Preferably, a 5'-O-glutaroyl derivative of vitamin B12 is formed by acylation of vitamin B12 with a reactive glutaric acid derivative to selectively convert the primary hydroxyl group (5'-OH) on the α-ribose moiety to a chemically reactive carboxyl group. The vitamin B12 derivative is then preferably reacted with a functional linker and/or spacer group to form a second derivative, which in turn is reacted with the therapeutic compound to form a biologically active conjugate.

It would have been obvious to one of ordinary skill in the art to produce an anti-tumor drug and cobalamin conjugate comprising a cobalamin, or a derivative or analogue thereof; a linker covalently bound to the 5'-OH moiety of cobalamin

or cobalamin derivative; and an anti-tumor drug covalently bound to the linker thereby forming the conjugate wherein the drug is cleavable from the linker and/or the linker is cleavable from the drug by an intracellular enzyme. Although Grissom is silent on the specific attachment of the components of the doxorubicin-cobalamin conjugate, Habberfield teaches that, in general, biologically active conjugates are prepared by reacting the therapeutically active compound with 5'-O-[glutaroyl]cyanocobalamin under conditions which form covalent bonds between the two. Preferably, a 5'-O-glutaroyl derivative of vitamin B12 is formed by acylation of vitamin B12 with a reactive glutaric acid derivative to selectively convert the primary hydroxyl group (5'-OH) on the α-ribose moiety to a chemically reactive carboxyl group. The vitamin B12 derivative is then preferably reacted with a functional linker and/or spacer group to form a second derivative, which in turn is reacted with the therapeutic compound to form a biologically active conjugate.

It would have also been obvious to one of ordinary skill in the art at the time of the invention to select a linker that is cleavable by an intracellular enzyme. Toki teaches that peptide-containing anticancer prodrugs have been developed that are activated by proteases within solid tumors. The drugs can be appended directly to the peptide, leading to prodrugs that can either release the parent drug or a drug that contains vestiges of the bound peptide. In the latter case, the released drug may have impaired cytotoxic activity. An additional consideration for direct drug attachment to peptides is the negative influence the drug can have on the kinetics of peptide hydrolysis. To circumvent these

potential shortcomings, an alternative approach for drug attachment incorporates the use of self-immolative spacers that spatially separate the drug from the site of enzymatic cleavage. The subsequent collapse of the incorporated linkers allows for the elimination of the fully active, chemically unmodified drug from the conjugate upon amid bond hydrolysis. One of the most commonly used spacers is the bifunctional p-aminobenzyl alcohol group, which is linked to the peptide through the amine moiety, forming an amide bond.

Furthermore, Dubowchik teaches peptide-DOX (doxorubicin) substrates that contain a self-immolative PABC spacer that are efficiently cleaved by cathepsin B to release free DOX but are very stable in human plasma. Cathepsin B is an attractive target for release of drugs from conjugates that are taken up by receptor-mediated endocytosis since it is ubiquitous and found in relatively high levels in mammalian lysosomes. In addition, several of these compounds release DOX on a time scale that may make them useful as prodrugs for metastatic or primary tumors that express extracellular cathepsin B. Indeed, in view of the teachings of the prior art the instantly claimed conjugates and methods for tumor treatment are obvious.

Conclusion

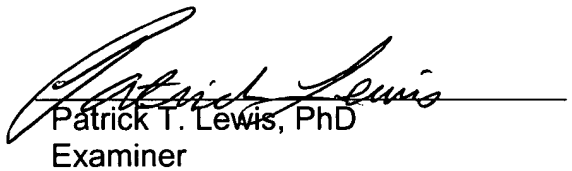
8. Claims 1-21 are pending. Claims 1-21 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Patrick T. Lewis, PhD
Examiner
Art Unit 1623

ptl